

REMARKS

Claims 1-18 are pending.

No new matter has been added by way of the above amendments.

For example, Applicants have amended claim 1 to remove the recitation of "virus-safe" and "selected from the group of interferons". Additionally, claim 1 has been amended to remove the recitation of "in an efficient amount to provide an extended shelf-life of the pharmaceutical composition". These amendments are non-narrowing and have been made in order to clarify the present invention. Claims 5 and 6 have been amended for purposes of antecedent basis only and these amendments are non-narrowing in nature. Claim 15 has been amended in order to depend upon claim 13. Claim 13 has been amended to remove the recitation of "virus-safe". New claim 16 is supported by originally filed claim 1 as well as the present specification at page 4, lines 2-8. New claims 17 and 18 are supported by the present specification at page 2, lines 10-16 and page 4, lines 10-15. Accordingly, no new matter has been added.

Applicants have attached hereto a marked up version of the claims to show the changes made for the Examiner's convenience.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

**Issues Under 35 U.S.C. §112, second paragraph**

The Examiner has rejected claims 1-15 under 35 U.S.C. §112, second paragraph for the reasons recited at page 4 of the outstanding Office Action. Applicants respectfully traverse the Examiner's rejection.

Applicants respectfully submit that the presently pending claims and the newly added claims fully satisfy the requirements of 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

**Issues Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1-15 under 35 U.S.C. §103(a) as being obvious over Georgiades et al., USP 4,732,683 (hereinafter referred to as Georgiades '683) in view of Manabe et al., USP 4,808,315 (hereinafter referred to as Manabe '315).

Applicants respectfully traverse the above rejection.

**The Present Invention and its Advantages**

The present invention relates to a method for preparing a pharmaceutical composition of a biologically active protein such as interferon. The composition prepared thereby is a "virus-safe" composition. In other words, composition is essentially free from substances, including viruses and prions, having a size in excess of 10 to 40 nm.

Distinctions Between the Present Invention and the Cited Art

The Examiner has cited Georgiades '683 since Geogrades '683 discusses the addition of non-ionic detergents to inactive Sendai virus or other contaminating viruses. However, Georgiades '683 fails to suggest or disclose subsequently treating the preparation with a filter for virus removal having a pore size of 10 to 40 nm. To cure this deficiency, the Examiner has relied upon the secondary reference of Manabe '315.

Applicants respectfully submit that the Examiner's combination of these two references is improper. Georgiades '683 teaches that inactivation of viruses in an interferon preparation by the addition of non-ionic detergent results in the destruction of a virus. However, Georgiades '683 fails to suggest or disclose the removal of viruses with a membrane filtration. It is known in the art that lipid-enveloped viruses may be inactivated by detergents in organic solvents. The viruses are inactivated due to solubilization of the lipid envelope of the protein.

However, detergents do not inactivate non-enveloped viruses, such as parvovirus and hepatitis A virus, which are resistant to detergents and various other physico-chemical treatments. The "membrane filtration" techniques taught by Georgiades '683 are ultrafiltration and sterile filtration aimed at concentrating protein solutions and removing bacteria. However, these filtration are not effective for the removal of viruses from interferon.

Nonetheless, the Examiner asserts that one would subsequently use a viral filtration step such as that disclosed by Manabe '315. This assertion is incorrect.

Georgiades '683 would not be able to effectively perform a subsequent viral filtration step using a pore size of 10 to 40 nm. This is due to the fact that Georgiades '683 stabilizes its compositions with albumin. However, as discussed in the present specification at page 2, line 26 to page 3, line 3, the use of stabilizers such as albumin results in inefficient removal procedures. For instance, virus removability of a virus removal filter decreases with increasing concentration of a coexisting protein such as albumin. This is evidently due to plugging of the filter with the coexisting protein.

Nonetheless, the Examiner asserts that it would have been *prima facie* obvious for one of ordinary skill in the art to first conduct the non-ionic detergent treatment of Georgiades '683 followed by the virus filtration of Manabe '315. However, as explained above, such a combination would destroy the effectiveness of the primary references of Georgiades '683. That is, if the albumin treated preparation of Georgiades '683 were to be subjected to the viral filtration of Manabe '315, the disadvantageous properties disclosed at page 2-3 of the specification would result. Citing references which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the

combination of claimed elements would have been obvious. Ex parte Hiyamizu, 10 USPQ2d 1393 (BPAI 1983). Such improper application of 103 is also applicable where the Examiner's proposed modification would render the prior art version unsatisfactory for its intended purpose. In re Gordon, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

Accordingly, in the present instance the Examiner's proposed modification of Georgiades '683 would render Georgiades '683 unsuitable. Thus, the Examiner cannot ignore the improper combination of Georgiades '683 with Manabe '315. In summary, Applicants respectfully submit that the Examiner has failed to present a valid *prima facie* case of obviousness for the present claims. Moreover, Applicants respectfully draw the Examiner's attention to claim 8 and newly added claims 16-18.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims. That is, Applicants have distinguished the presently claimed subject matter from the cited art. A Notice of Allowability is respectfully solicited.

#### **Finnish Priority Document**

At page 2 of the outstanding Office Action, the Examiner has stated that no copy of the certified copy of the Finnish priority document has been received. Applicants respectfully submit that in the present national stage application of PCT/FI99/00505, the

Serial No.: 09/701,031

International Bureau will supply a certified copy of the priority document.


If the Examiner has any questions or comments, please contact Craig A. McRobbie, Registration No. 42,874 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

1. (Amended) Method of preparing a [virus-safe] pharmaceutical composition of a biologically active protein [selected from the group of interferons], comprising the steps of

[-] adding to a solution of the protein a non-ionic detergent [in an efficient amount to provide an extended shelf-life of the pharmaceutical composition];

[-] subjecting the solution containing the non-ionic detergent to filtration on a virus removal filter with a pore size of 10 to 40 nm; and

[-] recovering the filtrate.

5. (Amended) The method according to any of claims 1 to 4, wherein the pharmaceutical composition comprises [the] a solution of purified  $\alpha$ -interferon.

6. (Amended) The method according to any of claims [1] 5, wherein [the activity of] the  $\alpha$ -interferon solution before virus filtration [is], has an activity in the range of 3 to 50 mill. IU/ml.

13. (Amended) [A virus-safe] An  $\alpha$ -interferon composition,

comprising a non-ionic detergent as a stabilizer in an amount exceeding the critical micellar concentration of the detergent and being essentially free from substances and agents retained on a virus-filter having a high virus retentive capacity even for small non-enveloped viruses.

15. (Twice Amended) The composition according to claim [1] 13, comprising an  $\alpha$ -interferon solution containing at least two  $\alpha$ -interferon subtypes selected from the group consisting of  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 4$ ,  $\alpha 7$ ,  $\alpha 8$ ,  $\alpha 10$ ,  $\alpha 14$ ,  $\alpha 17$  and  $\alpha 21$ .

Claims 16-18 have been added.